REMARKS

Reconsideration and withdrawal of the rejections to the claims and consideration and entry of this paper are respectfully requested in view of the herein remarks, which place the application in condition for allowance.

I. STATUS OF CLAIMS AND FORMAL MATTERS

The applicants appreciate the Examiner's acknowledgement of allowable subject matter with respect to claims 4, 5, 7, 11 and 24. The applicants note that claims 1-3, 9 and 10 were objected to as containing non-elected subject matter. While the applicants do not concede that the restriction was proper, the non-elected subject matter has been cancelled from claims 1-3, 9 and 10; the applicants reserve the right to file a divisional application to further pursue this cancelled subject matter.

Claim 8 has also been corrected to the 112, second paragraph rejection which is explained separately below.

Claims 14-22 have been withdrawn from consideration, however, as previously noted by the applicants in their 3 February 2006 response, these claims are subject to rejoinder as they are directed to the method of using (claims 14-19) and method of making (claims 20-22) the compounds currently under examination.

Therefore, it is presumed that there are no remaining issues preventing a Notice of Allowance to be granted for claims 1-5, 7-11, 14-22 and 24.

The only remaining issue which needs to be addressed is the rejection of claims 12, 13, 25 and 26 for lack of enablement. Claims 1-5, 7-22, and 24-26 are still pending in this application. No new matter has been added.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited in the Office Action, and that these claims were in full compliance with the requirements of 35 U.S.C. § 112. The amendments of the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled.

II. THE 35 U.S.C. 112, 2ND PARAGRAPH REJECTION HAS BEEN OVERCOME

Claim 8 was rejected because the definition for X_1 appeared to be open ended. This was due to a typographical error which has now been corrected. Claim 8 has been amended to --- X_1 is a carbon atom or a nitrogen atom--- which is consistent with the scope of the other compound claims of the invention.

III. THE 35 U.S.C. 112, 1ST PARAGRAPH REJECTION HAS BEEN OVERCOME

Claims 12, 13, 25 and 26 have been rejected as allegedly failing to be enabling for the treatment of all cancers. The applicants respectfully request reconsideration for the following reasons.

Background

The rejection acknowledges that the applicants have provided an enabling disclosure for "certain cancers" and the rejection appears to be based on the speculation that the applicants' disclosure may not be operative for ALL cancers.

However, "[i]n order to make a [lack of enablement] rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." *See MPEP 2164.04*. This burden has not been met and requiring that the applicants show evidence of operability for all possible permutations of the applicants claimed invention is not the proper standard for determining whether the applicants' invention is enabling. As stated in MPEP 2164.08:

> The presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The *standard is whether a skilled person could determine which embodiments* that were conceived, but not yet made, *would be inoperative or operative with expenditure of no more effort than is normally required in the art. Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling)...
>
> ...A disclosure of a large number of operable embodiments and the identification of *a single inoperative embodiment* did not render a claim broader than the enabled scope because *undue experimentation was not involved in determining those embodiments that were operable. In re Angstadt*, 537 F.2d 498, 502-503, 190 USPQ 214, 218 (CCPA 1976)." (emphasis added)

The applicants request reconsideration of the lack of enablement rejection because:

(1) no evidence presented by the Examiner which teaches or suggests that one or more embodiments of the applicants invention is inoperative for the treatment of cancer; and

(2) even if such evidence were presented, no evidence has been presented which shows that identifying the inoperative embodiment would require undue experimentation by one of ordinary skill in the art.

(1) No evidence of inoperability for the treatment of cancer has been presented

One of ordinary skill in the art would not find credible the assertion that the entirety of the pharmaceutical arts, which includes such well-known treatments like pain relief with aspirin and ibuprofen, anti-biotic effects with drugs such as erythromycin, etc. as being "unpredictable" without supporting evidence. With this generic statement, the Examiner infers that the applicants' invention with respect to the inhibition of cyclin dependent kinases (Cdks) and cancer treatment is highly unpredictable but offers no evidence to support this hypothesis.[1] Moreover, one of ordinary skill in the art would not view inhibition of Cdks or the treatment of cancer as being a "nascent technology" which requires enablement by a "specific and useful" teaching. *See MPEP 2164.03.*

To the contrary, the overwhelming evidence in the art acknowledges that the treatment of cancers via inhibition of Cdks is well known and accepted by those of ordinary skill in the art. The applicants' "Background of the Invention" section clearly establishes that the state of the art recognized a correlation between Cdks and cancer treatment. The Declaration by Dr. Kalpana Joshi (Director of Oncology at Nicholas Piramal India Ltd.) states on page 3 that "...several cell cycle regulators are factors involved in human cancers and among the cell cycle regulators, Cdks appear to be the most promising ones for pharmacological intervention."

The Joshi declaration also cites a number of references available to those of ordinary skill in the art at the time this invention was filed which clearly support the role of CDKs in the development of cancers and that data for Cdks as anticancer agents had been reported in the art: Sausville et al., *The Oncologist*, vol. 6: 517-537 (2001); Parker, B.W., *Blood*, vol. 91(2): 458-465 (1998); Sausville, *Pharmacol. Ther.*, vol. 82: 285-292 (1999); and Meijer, L., *Pharmacol. Ther.*, vol. 82: 279-282 (1999) - see pages 4-5 of the Joshi Declaration.

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[1] *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) stands for the general proposition that unpredictable arts require more enablement. However, it has not been established that cancer treatment or inhibition of cyclin dependent kinase would be considered unpredictable to those of ordinary skill in the art. Moreover, *In re Fisher* is also cited in MPEP 2164.08, being indicative that "scope of enablement" must only bear "a reasonable correlation" to the scope of the claims.

Even the references cited by the Examiner as "evidence" for unpredictability fail to support his position and actually serves to buttress the applicants' position. Dr. Joshi's Declaration states on pages 3-4:

> "The two references: Davies (Pharmacology & Therapeutics, 2002, 125-133) and Toogood (Medicinal Research Reviews, 2001, 487-498) cited by the examiner also ascertain the nexus between Cdks and cancer. For instance, Davies emphasises that strong genetic link between Cdks and the molecular pathology of cancer has provided the rationale for developing small-molecule inhibitors of Cdks. The Toogood reference briefly reviews the use of a class of pyrido[2,3-d]pyrimidines compounds as Cdk inhibitors. Although, both these reference do not provide actual data for treatment of cancer, they ascertain that the inhibitors of cyclin-dependent kinases possess therapeutic utility against a wide variety of proliferative diseases, especially cancer. "

As noted above, the initial burden is on the Examiner to establish the elements supporting a holding of undue experimentation. As such, it ***is not*** necessary for the Davies and Toogood references to affirm the applicants' assertion of cancer treatment. It ***is*** necessary, for the Examiner to establish a lack of enablement rejection, for Davies and Toogood (or some other reference) to affirmatively show that the applicants' assertion of cancer treatment was in doubt. Davies and Toogood is silent on the issue of cancer treatment and therefore, fails to affirmatively establish this doubt.

The Examiner also refers to Table 2 in the applicants' specification which shows activity and toxicity levels of applicants' compounds. The Examiner interprets Table 2 to mean that the tested compounds are inactive against MDAMB-231 breast cell lines and H640 lung cell lines. This is because the compounds are stated as 'NT' against these particular cell lines and NT is defined as non-toxic, having 30% or less toxicity. The Examiner apparently assumes that if there is no toxicity, there would also be no activity given that there is always a degree of toxicity with any active pharmaceutical.

In this regard, the applicants wishes to draw the examiner's attention to pages 7-8 of Joshi's Declaration wherein Dr. Joshi has mentioned that the toxicity of the representative compounds against the human breast carcinoma MDA-MB-231 and lung carcinoma H-460 cell lines was mentioned as non-toxic i.e. $\leq$ 30 % only at a concentration of 1 μM of the compounds for a period of 48 hours. Dr. Joshi further states that this should not be misinterpreted to mean that the compounds are not cytotoxic because in the ^{3}H-Thymidine uptake experiment the compounds exhibit anti-proliferative activity at the same concentration.

The Joshi declaration has also provided evidence that the hydrochloride salt of (+)-*trans*-2-(2-chloro-phenyl)-5,7-dihydroxy-8-(2-hydroxymethyl-1-methyl-pyrrolidin-3-yl)-

chromen-4-one ("a representative compound") exhibits anti-cancer activity against the said cell lines.

(2) No evidence that even if an inoperative element was identified that such identification would require undue experimentation by one of ordinary skill in the art

Even if the Examiner could somehow show by a preponderance of the evidence (which now requires a greater evidentiary hurdle in light of the arguments and evidence presented by the applicants in this response) in his next Office Action that some aspect of the applicants' invention was inoperative for the treatment of cancer, the Examiner still has the additional burden of showing why one of ordinary skill in this art would be unable to identify the inoperative elements without undue experimentation.

The Examiner contends that the present invention is not enabled because the quantity of experimentation needed is undue experimentation. However, the Examiner appears to misinterpret the nexus between ***quantity*** of experimentation and ***undue*** experimentation. As noted in *In re Wands*:

> "The [experimentation] test is not merely quantitative, since a ***considerable amount of experimentation is permissible, if it is merely routine***, or if the specification in question provides a ***reasonable amount of guidance*** with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976))." (emphasis added)

As such, the applicants' respectfully disagree with the Examiner's contention that the quantity of experimentation necessary would be viewed as undue to one of ordinary skill in the art. The basis for the applicants' position is as follows.

First, there is enough teaching in the specification to demonstrate that the compounds exhibited cyclin dependent kinases inhibiting activity (see Table 1 in the specification). Also in Table 2 the applicants have provided data which demonstrate that the compounds exhibit anti-cancer activity against a number of cancer cell lines. However, it would be improper to restrict scope of the claims to those cell lines which were merely included as being representative examples to demonstrate the anti-cancer activity of the compounds of the present invention. As noted in MPEP 2164.08 - "...not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted. (*In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991))." There has been no basis in fact as to why the applicants are required to test for every possible type of cancer.

Second, the state of the art at the time of the applicants' invention was filed, clearly indicate that compounds exhibiting CDK inhibiting activity were useful as anticancer agents and that assays for determining such activity were well known. Page 4 of Dr. Joshi's declaration further supports this position with the citation of a number of references which clearly indicate that a compound exhibiting CDK inhibiting activity demonstrate anti-cancer activity against several cell lines.

Third, the Joshi Declaration at pages 5-7 has provided additional data to demonstrate that the compounds of the present invention exhibit anti-cancer activity against a number of cancer cell lines. Dr. Joshi carried out further experimentation involving testing of hydrochloride salt of (+)-*trans*-2-(2-chloro-phenyl)-5,7-dihydroxy-8-(2-hydroxymethyl-1-methyl-pyrrolidin-3-yl)-chromen-4-one ("a representative compound") against different cancer cell lines and the data for which is provided in Table 2 on pages 6-7 of the Joshi declaration.

Given that the applicants and the state of the art show a correlation between inhibition of Cdks and cancer treatment and that the assays for testing anti-cancer activity are also well-known in the art, one of ordinary skill in the art would not be forced to undergo undue experimentation to determine any inoperative embodiments of the invention.

CONCLUSION

Considering the nexus between Cdks and the development of cancer and in view of the foregoing, the applicants contend that the specification is enabling for treatment of all cancers and hence, the rejection under 35 U.S.C. 112, 1st paragraph can be withdrawn.

In view of the remarks and amendments herewith, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date, and, the Examiner is invited to telephonically contact the undersigned to advance prosecution. The Commission is authorized to charge any fee occasioned by this paper, or credit any overpayment of such fees, to Deposit Account No. 50-0320.

Respectfully submitted,
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